

Relation between infarct size and ventricular arrhythmia¹

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In order to determine whether ventricular arrhythmia is quantitatively related to infarct size estimated enzymatically we studied 31 patients with acute myocardial infarction without cardiogenic shock. Infarct size index was estimated from hourly serum creatine kinase (CK) changes during periods of 48 to 72 hours. Ventricular arrhythmia was quantified by automated analysis of continuous electrocardiographic recordings over a period of 20 hours with the use of the Argus/H computer system. Patients were classified into three groups according to infarct size index. Patients in all groups had similar average heart rate, blood pressure, serum potassium, and arterial pH and PCO₂ values during the first 10 hours after admission. The total number of ventricular ectopic beats (VEB), frequency of couplets, and ventricular tachycardia, and peak rate of ventricular ectopic beats during the first 10 hours after admission were all related to infarct size index. For example, patients with small, medium, and large estimated infarct size averaged 26, 104, and 405 ventricular ectopic beats, respectively. These results suggest that the severity of ventricular arrhythmia early after myocardial infarction is related to the extent of myocardial injury as estimated enzymatically. Thus the apparent efficacy and therefore the evaluation of antiarrhythmic agents early after myocardial infarction may be influenced by the magnitude of injury sustained by the heart.

Despite considerable progress in the management of ventricular arrhythmia associated with acute myocardial infarction a substantial hospital mortality and a high incidence of sudden death after hospital discharge persist (Killip, 1971; Spracklen *et al.*, 1968; Grace and Yarbote, 1971). Identification of specific factors associated with ventricular arrhythmia in patients with myocardial infarction is of potential importance from at least two points of view. Firstly, it may help to focus treatment more effectively on the cause of the arrhythmia rather than on its manifestations. Secondly, it should facilitate objective assessment of antiarrhythmic agents by helping to define subsets of patients at comparable risk.

Since the extent of infarction was one factor likely to be associated with the incidence and severity of ventricular arrhythmia and since infarct size can be estimated from analysis of serial changes in serum CK activity (Sobel *et al.*, 1972) the present study was designed to determine whether ven-

tricular arrhythmia in patients with myocardial infarction correlates with the extent of injury sustained by the heart estimated in this fashion. Though a relation between ventricular arrhythmia and infarct size has not been explicitly emphasized, proximal coronary artery occlusion in animals produces ventricular fibrillation more often than distal occlusion, which latter presumably results in less extensive infarction (Allen and Laadt, 1950), and susceptibility to arrhythmia in animals with coronary occlusion at selected sites may depend on the severity of myocardial electrolyte alterations (Harris *et al.*, 1954), perhaps related to the site or overall extent of infarction (Thomas, Shulman, and Opie, 1970). The association between the amount of rise in serum transaminase and lactic dehydrogenase and the extent of the myocardial infarct found at necropsy was recognized by Kibe and Nilsson (1967). These investigators related peak serum enzyme values to mortality in another series of patients reported in the same study. Though the explicit association between ventricular arrhythmia and infarct size was not emphasized, the authors' observed correlation of mortality with peak serum

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enzyme levels suggests that arrhythmia leading to death may have occurred more often in patients with larger infarcts. Chapman (1972) observed an association between the incidence of both supra-ventricular and ventricular arrhythmia and the magnitude of the rise in serum transaminase levels in a prospective study of patients with myocardial infarction, in concert with retrospective observations by others that patients with infarction associated with a substantial increase in serum transaminase activity exhibit particularly severe arrhythmia (Mogenssen, 1970). Severe arrhythmia is more commonly seen with transmural infarction (Skaeggestad, 1973), and recently ventricular arrhythmia was found to be more prominent in patients with a distinctly raised electrocardiographic ST segment (Nielsen, 1973). These observations, considered together, suggest that infarct size contributes directly or indirectly to the severity of early ventricular arrhythmia.

In the present study the severity of early ventricular arrhythmia in 31 patients with acute myocardial infarction was evaluated by automated analysis of continuous electrocardiographic recordings over a 20-hour period and this was compared with the extent of damage sustained by the heart as estimated from serial changes in serum CK activity.

Patients and methods

Thirty-one patients admitted to the Barnes Hospital cardiac care unit with acute myocardial infarction, manifested by typical chest pain, serial serum enzyme changes, and electrocardiographic changes diagnostic of transmural infarction, were studied. Patients were included in the study only if the onset of symptoms was ≤ 6 hours before admission. In order to avoid spurious estimates of infarct size due to release of CK from non-cardiac sources into the circulation patients with shock and those who had received intramuscular injections before admission were excluded. An additional 18 patients with coronary artery disease and suspected but unconfirmed acute myocardial infarction were also studied. In all patients studied conventional therapy with bolus injections of lignocaine was employed to treat 10 or more ventricular ectopic beats (VEB) per minute occurring for two consecutive minutes, more than three VEB in a row, or VEB occurring on the ascending limb of the T wave.

Assessment of ventricular arrhythmia

Ventricular arrhythmia was detected and quantified on 20-hour continuous electrocardiographic Holter tape recordings analysed with the Argus/H computer system. Recordings were initiated in all cases within one hour after admission. All recorded ventricular complexes were analysed by the computer. Ventricular ectopic beats were verified with an editing system previously

described (Nolle *et al.*, 1974). The reproducibility of the combined computer and editing system has previously been shown to be within 1 per cent (Nolle *et al.*, 1974).

Recordings during the first and second 10-hour period intervals after admission were analysed separately for each patient to determine the total number of VEB in each period, the number of episodes of couplets and ventricular tachycardia (defined as three or more VEB in a row) during each period, and the peak frequency of VEB during any 15-minute period.

Estimation of infarct size

Infarct size was estimated by analysis of hourly serum CK and CK isoenzyme changes as previously described (Sobel *et al.*, 1972; Shell, Kjekshus, and Sobel, 1971). To avoid repetitive venepuncture blood samples were obtained with the use of an intravenous heparin lock. Results were expressed as CK-gram-equivalent per sq. metre body surface area (CK-g-eq/m²).

The enzymatic method of estimating infarct size is based on the concept that serial changes in serum CK activity after myocardial infarction reflect two competing phenomena: (1) release of enzyme from irreversibly injured myocardium, and (2) disappearance of enzyme from blood conforming to assumed first order kinetics. Infarct size is estimated by calculating cumulated CK released and by taking into account the estimated amount of CK lost from 1 g of myocardium undergoing homogeneous necrosis. Nevertheless, this method has significant inherent limitations. The fractional disappearance rate of CK (k_d) from the circulation varies substantially among individual patients. This can be accounted for in part, as pointed out recently by Norris *et al.* (1975), by individualization of estimated k_d based on analysis of descending portions of serial serum CK curves in patients sustaining myocardial infarction. We have recently shown that haemodynamic perturbations simulating those associated with myocardial infarction do not alter k_d substantially and, furthermore, that repetitive determinations of k_d in the same conscious animal on successive days or during intercedent myocardial infarction lead to results with a variance of less than 10 per cent (Roberts, Henry, and Sobel, 1975). Thus, though estimates of infarct size could be altered if k_d varied, k_d seems to be relatively uninfluenced by the effects of haemodynamic perturbations.

It is important to recognize that enzymatic estimates of infarct size may be distorted by alterations in the proportion of CK released into the circulation compared to that lost from the heart. Experimentally this ratio has been observed to be low with a value of 0.15 ± 0.016 (range) (Roberts *et al.*, 1975). Though the mechanisms responsible for the low value of this ratio have not yet been thoroughly elucidated the results of preliminary experiments in our laboratory suggest that one important factor may be inactivation of CK in lymph during transit from necrotic myocardium to the peripheral circulation (unpublished observations). Regardless of what mechanisms account for the low released/depleted ratio, variation in the ratio among patients could lead to distorted estimates of infarct size in clinical studies.

TABLE Patients grouped by infarct size index

	Group 1 1 < ISI < 25 ¹	Group 2 25 < ISI < 50	Group 3 ISI ≥ 50
Number of patients	9	12	10
Heart rate (beats/min)	78 ± 4	75 ± 8	75 ± 7
Systemic arterial blood pressure (kPa)	16/9.8	15.4/10.5	14.6/10
(mm Hg)	120/74	116/79	110/75
Plasma potassium (mmol/l)	4.1 ± 0.1	4.1 ± 0.1	4.1 ± 0.2
Arterial			
pH	7.5 ± 0.1	7.4 ± 0.1	7.5 ± 0.1
PCO ₂ (kPa)	3.9 ± 0.3	4.5 ± 0.3	4.0 ± 0.1
PO ₂ (kPa)	11.2 ± 0.8	11.7 ± 2.1	9.8 ± 1.2
Norris prognostic index ²	5.1 ± 0.8	5.7 ± 0.8	8.4 ± 1.1
Patients requiring bolus lignocaine (%)	44%	50%	60%

Results are expressed as average values (mean ± SD) during the first 10 hours after admission.

¹ISI = infarct size index expressed as CK-gram-equivalents/m² of body surface area.

²Norris *et al.*, 1969a.

Conversion: SI to Traditional Units: PCO₂ and PO₂ 1 kPa ≈ 7.5 mmHg.

One other parameter which influences the value obtained in enzymatic estimation of infarct size is the estimate of distribution volume for the enzyme. In our initial studies (Shell *et al.*, 1971) this was estimated from experiments in conscious dogs in which myocardial CK was injected intravenously and the distribution volume calculated by the dilution principle. Recently, evaluation of the distribution volume with enzyme prepared under conditions to reduce lability of injected CK led to consistent results in which distribution volume was found to approximate to plasma volume (4.5 to 5.5 per cent of body weight, range) (Roberts *et al.*, 1975). If the distribution volume of CK differed from plasma volume in a specific patient, however, or if plasma volume represented a substantially different proportion of body weight than is generally the case, enzymatic estimates of infarct size would be distorted.

Results

Classification of patients according to estimated infarct size

The patients with myocardial infarction included in this study were divided into three groups on the basis of the estimated extent of infarction. Group 1 consisted of patients with an estimated infarct size index of from 1 to 24.9; group 2, those with an index of from 25 to 49.9; and group 3, those with an index exceeding 50 CK-g-eq/m². Patients in all three groups had generally similar average heart rate, blood pressure, serum potassium, and arterial pH and PCO₂ values during the first 10 hours after admission (see Table). Pulmonary arterial wedge pressure was generally not monitored in order to avoid influencing the occurrence of ventricular arrhythmia. The only exceptions were two patients in group 3 who required pulmonary arterial wedge pressure determinations for clinical management.

Patients with larger infarcts exhibited more severe manifestations of infarction as reflected by increased values for the Norris coronary prognostic index, previously shown to be associated with poor prognosis (Norris *et al.*, 1969a; Norris, Brandt, and Lee, 1969b). Group 3 patients had modest hypoxaemia and more often required bolus injections of lignocaine, which may have reduced the incidence of ventricular arrhythmia in those with larger infarcts.

The relatively modest derangements in systemic arterial blood pressure, arterial blood gases, and blood electrolytes suggest that differences in ventricular arrhythmia early after admission among these three groups of patients were not secondary exclusively to impaired left ventricular function or its systemic sequelae.

Relationship between ventricular arrhythmia and extent of infarction

The incidence of ventricular ectopic beats detected by the Argus/H computer system during the initial 20 hours after admission differed strikingly when patients with suspected but unconfirmed myocardial infarction were compared to those with definite acute myocardial infarction. Patients with unconfirmed myocardial infarction had fewer VEB, particularly during the first 10 hours (Fig. 1). Furthermore, as expected, patients with infarction exhibited significantly more VEB during the first compared with the second 10 hours after admission in contrast to patients without infarction, who exhibited a relatively constant incidence of VEB during the two periods. These results, while not unexpected, are presented to illustrate the efficiency

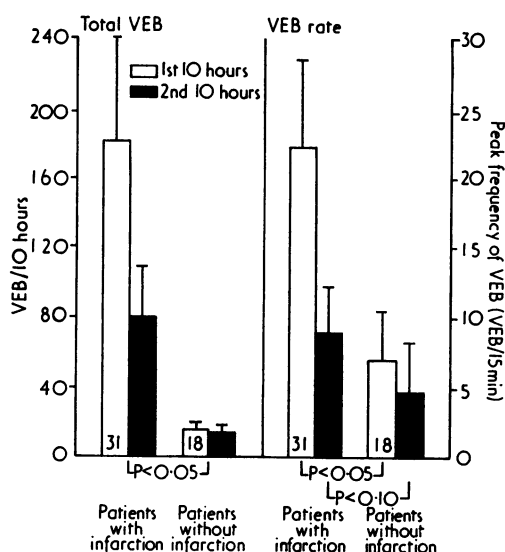


FIG. 1 Total VEB and peak VEB rate in patients with and without acute myocardial infarction. Total VEB and peak VEB rate during first 10-hour period after admission shown as open bars. Corresponding values in second 10-hour period shown as shaded bars. Vertical lines in this and subsequent figures indicate mean \pm standard error.

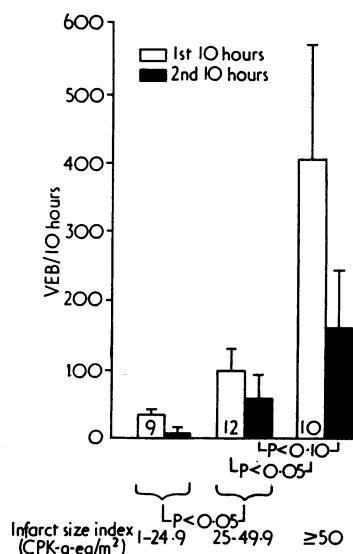


FIG. 2 Relation between total number of VEB and infarct size index estimated from serial changes in serum CK activity. Incidence of VEB was higher in patients with larger estimated infarct size in both first and second 10-hour periods after admission.

of the computer system in detecting VEB in patients with confirmed infarction.

The number of VEB exhibited by patients with myocardial infarction during either the first or the second 10-hour period after admission was directly related to the infarct size index estimated from serial serum CK changes (Fig. 2). Thus during the first 10 hours after infarction the total number of VEB averaged 26, 104, and 405 in groups 1, 2, and 3 respectively. A similar trend was evident when total VEB during the second 10-hour period after admission was compared to infarct size index in each group, though the generally decreased incidence of arrhythmias later in the course tended to reduce differences between the groups. The difference in total VEB during either the first or second 10-hour period in group 1 compared with group 2 patients was significant at the 0.05 level. Thus patients with larger infarcts had a larger number of VEB early after the onset of infarction.

Similar trends were apparent in the incidence of couplets and ventricular tachycardia and in the peak rate of VEB. The incidence of couplets and ventricular tachycardia during the first 10 hours after admission was related to estimated infarct size (Fig. 3). The peak rate of VEB during the first 10 hours after admission, expressed as the maximum

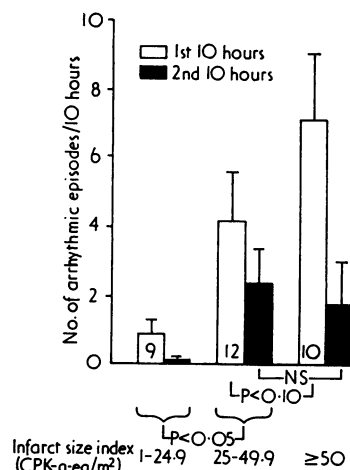


FIG. 3 Relation between the incidence of couplets and episodes of ventricular tachycardia and estimated infarct size in patients with acute myocardial infarction. During first 10-hour period after admission the incidence of arrhythmic episodes was proportional to estimated infarct size index. During second 10-hour period patients with smallest estimated infarct size index had lowest incidence of episodes of ventricular arrhythmia.

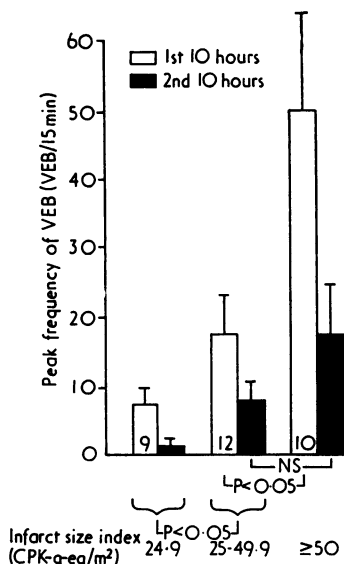


FIG. 4 Relation between the maximum number of VEB (during any 15-minute interval) and infarct size index. Peak VEB incidence during first or second 10-hour periods after admission was increased in patients with larger estimated infarct size.

number during any 15-minute interval, was also related to infarct size index (Fig. 4). Again, patients with larger infarcts had higher peak VEB rates.

Since these results indicated that premature ventricular beats early after infarction are directly related to infarct size we sought to determine whether the incidence of VEB occurring later in the recovery period was similarly related to the extent of myocardial injury. Among 14 patients from whom 10-hour follow-up recordings were obtained one to nine months after the initial infarction only rare episodes of couplets or ventricular tachycardia were evident (Fig. 5), though in each case no anti-arrhythmic medication had been taken for at least one week before the recording. Perhaps because of the low incidence of late ventricular arrhythmia in patients with small, medium, and large infarct, no clear-cut relation was discernible between late ventricular arrhythmia and infarct size estimated at the time of the acute illness. An increased incidence of late sudden death could have occurred in those patients with frequent VEB during the follow-up interval leading to bias in the sample of surviving patients. But we have no direct evidence to support this possibility.

Discussion

The results of this study corroborate previous

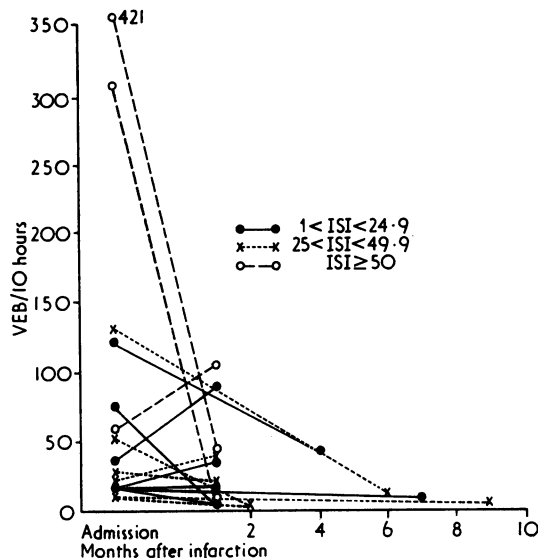


FIG. 5 Total number of VEB in a 10-hour period in 14 patients recorded one to nine months after admission for acute myocardial infarction. Despite wide disparity in incidence of VEB in first 10 hours after initial hospital admission most patients in this group had a low incidence of VEB in follow-up recordings. Thus no close relation was discernible between infarct size and late ventricular arrhythmia.

observations indicating an association between the extent of myocardial infarction and the incidence of ventricular arrhythmia. In this prospective series in which arrhythmia was quantified by automated analysis of all QRS complexes on 20-hour continuous electrocardiographic recordings the incidence of ventricular arrhythmia early after acute myocardial infarction was related to infarct size estimated from serial changes in serum CK activity. The association between the two is compatible with previous observations (Allen and Laadt, 1950; Kibe and Nilsson, 1967; Thomas *et al.*, 1970; Mogensen, 1970; Chapman, 1972; Skaeggestad, 1973; Nielsen, 1973), and ample precedent suggests an association between the extent of infarction and the prevalence of ventricular arrhythmia.

Experimentally we have recently observed a correlation between infarct size in dogs and the extent of reduction of the threshold to ventricular fibrillation, again suggesting a relation between the magnitude of an ischaemic insult to the heart and electrical instability (Bloor *et al.*, 1975). We have previously shown that infarct size estimated from serum CK changes is a useful index of the likelihood of impairment of ventricular function after myocardial infarction (Kostuk *et al.*, 1973). Others have

shown a correlation between infarct size estimated by this technique and altered ventricular function during the acute illness (Norris *et al.*, 1975; Mathey *et al.*, 1974) and with the extent of damage assessed morphologically in patients who fail to survive the acute episode (Bleifeld, Mathey, and Hanrath, 1974). The present findings suggest that the extent of infarction may influence the incidence and nature of ventricular arrhythmia as well as of impaired ventricular function early after infarction. If both reflect a common underlying factor, such as infarct size, it would, of course, follow that arrhythmia and impaired cardiac performance would not be independent but rather associated phenomena.

An indirect mechanism could be responsible for the association between arrhythmia and infarct size, such as an increase in circulating catecholamines (Jewitt *et al.*, 1969) or free fatty acids (Oliver, Kurien, and Greenwood, 1968) in response to haemodynamic impairment associated with extensive infarction. However, the different incidence of ventricular arrhythmia in patients in group 1 compared with those in group 2 despite similar heart rate, blood pressure, and coronary prognostic indices in both suggest that a more direct mechanism may play an important role. Recent observations of surviving Purkinje cells on the endocardial surface of infarcts in animals and patients (Fenoglio *et al.*, 1974) suggest the possibility that the overall quantity of electrically unstable cells could depend on the overall extent of infarction and could in turn be a determinant of early ventricular arrhythmia. On the other hand, the increased potentiality for re-entry rhythms in large masses of myocardium undergoing infarction could be responsible for the observed relationship (Surawicz, 1971). Heterogeneity of potassium or catecholamine concentrations, altered responsiveness, or other local myocardial factors could account for the relation between infarct size and arrhythmia observed in the present study (Opie *et al.*, 1973).

Since the severity of ventricular arrhythmia seems to be correlated with infarct size, even in patients with clinically uncomplicated myocardial infarction, the infarct size must be considered when assessing the value of antiarrhythmic agents given early after the onset of infarction. In addition, the possibility that effective antiarrhythmic therapy may depend in part on limitation of the evolution of infarction itself as well as on pharmacological suppression of ventricular ectopic rhythms deserves exploration. Perhaps more importantly clarification of the mechanisms by which infarct size influences ventricular arrhythmia may shed light on mechanisms accounting for sudden death in ambulatory individuals as well.

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